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Progestogen Supplementation during Luteal Phase in the Treatment of Infertility in the First Trimester

Manish R Pandya[1]*, Chirag Amin[2], Ganpant Sawant[3], Sunita Chandra[4], Vasundhari Mandi[5] and Suman Lal[6]

[1]Mahavir Hospital, Surendranagar, Gujarat, India

[2]Amin's Hospital, Ahmedabad, Gujarat, India

[3]D Y Patil Medical College, Mumbai, Maharashtra, India

[4]Rajendra Nagar Hospital, Lucknow, Uttar Pradesh, India

[5]Sanjeevni maternity and infertility hospital, Raichur, Karnataka, India

[6]Max hospital, Gurgaon, Haryana, India

***Corresponding author:** Manish Pandya, Scientific Research Institute, Surendranagar – 363001, India, Tel: 9825223816; Email: drmanish.pandya@gmail.com

Review Article

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Abstract

Aim: The aim of present review is to provide a comprehensive view of the literature regarding the clinical efficacy and safety effects of supplementation of Progestogens during luteal phase in the first trimester.

Methods: A literature search was performed using electronic databases like Pub med/Medline to identify from 1980 to 2015. The search yielded around 27 original studies and review articles. The search yielded around 31 clinical studies and reviews.

Results: Progestogen use for luteal support in assisted reproductive technologies is associated with significantly higher rates of live birth or ongoing pregnancy than placebo or no treatment. Based on findings from randomized control studies and meta-analysis, similar ongoing pregnancy and miscarriage rates have been observed for dydrogesterone (oral) when compared to intra-vaginal micronized progesterone (MCP) and between MCP intra-vaginal and MCP intra-muscular for luteal phase support. However, dydrogesterone (oral) exhibited an overall higher ongoing pregnancy rate compared to MCP oral (30% vs. 11%). There was no evidence to indicate that maternal exposure to Progestogens during pregnancy increased the risk for birth defects.

Conclusion: The relative effectiveness, safety, optimal route and duration of oral, vaginal, and intra-muscular progestogen formulations is a topic of ongoing debate. Future investigations with longer follow-ups and larger sample sizes comparing different routes of administration, dosages, and timing of administration are warranted.

Keywords: Progestogens; Infertility; Iuteal Phase Support; Iuteal Phase Defect; In-vitro Fertilization; Intra-Uterine Insemination

Introduction

Infertility is an important condition in reproductive medicine with physiologic, economic, demographic and medical implications. It is clinically described as inability of a person or a couple to conceive after one year of unprotected intercourse or inability of the female to carry pregnancy to term [1]. Infertility is called 'primary infertility' if the woman is unable to ever become pregnant or to carry a pregnancy to a live birth. If a woman is not able to bear a child following a previous pregnancy or a pregnancy leading to a live birth, it is termed as 'secondary infertility' [2]. In India the infertility rate is reported to be about 8% [3,4]. In most cases, the etiology is distributed fairly equally among male factors, ovarian dysfunction, and tubal factors. A smaller percentage of cases are attributed to endometriosis, uterine or cervical factors, or other causes. However, in approximately one fourth of couples, the cause is uncertain and is referred to as "unexplained infertility" [5].

The first step of treating infertility is to treat the underlying cause of infertility, on the basis of which varied categories of treatment options are available such as medications; surgical treatments, and assisted reproductive technology (ART) [6]. Various factors, including pituitary down regulation with gonadotropin-releasing hormone (GnRH) agonist, administration of HCG for final oocytes maturation, and aspiration of follicular fluid in ART may alter the estrogen/progesterone ratio, resulting in luteal phase defect [7-9]. Studies have established that luteal function is compromised in in-vitro fertilization (IVF) cycles wherein the absence of luteal phase support (LPS) leads to premature luteolysis and early bleeding thereby, resulting in a significant reduction in pregnancy rates [10-14]. Hormone supplementation becomes utmost crucial during ART as the use of GnRH agonist or GnRH antagonists for pituitary down regulation disturbs the normal progesterone production [10]. Progesterone supplementation during the luteal phase of the IVF cycles improves clinical pregnancy outcomes significantly as compared to cycles without treatment [15]. Progesterone is usually the drug of choice for luteal support as progesterone produced by corpus luteum activates a cascade of molecular events that renders the endometrium receptive to implantation and potentially sustains the survival of the embryo [16-18]. Over the past few years progesterone supplementation has been extensively investigated to overcome LPD in IVF cycles [19,20]. Available products include both 'synthetic' and 'natural' progesterone which can be administered orally, intramuscularly (IM), rectally, or intra-vaginally (IV) for LPS [15,21]. The aim of this descriptive review is to provide an overview of current scientific evidence, summarizing the clinical efficacy and safety of progestogens available for LPS during intra-uterine insemination (IUI) and IVF cycles in the first trimester.

Methods

A literature search was performed using electronic databases such as Pubmed/Medline to identify relevant articles using relevant search terms for Progestogens, infertility, LPS, ART, IUI and IVF. From this search, publications that met the following criteria:-original contributions of Progestogens with relevant product names, randomized control trials, observational studies, along with the review articles, systematic reviews and meta-analyses and reports limited to clinical human data that were published in the English language were included in the review. Case reports and case series were not included in the review. All articles considered were published in the scientific literature. Full text articles of relevant abstracts were assessed and evaluated. The search yielded around 31 original studies (randomized controlled, open and observational), systematic reviews and meta-analysis evaluating clinical efficacy and/or safety of Progestogens in management of infertility which were reviewed and are included in the subsequent sections below.

Results

Role of Progestogens in Intra-Uterine Insemination (IUI)

IUI is considered to be an intermediate step before application of sophisticated assisted reproductive techniques like IVF [22]. Following IUI, Progestogens are prescribed to supplement the luteal phase to facilitate better implantation of the embryo and sustenance of pregnancy in ART [23]. A recent randomized double blind clinical trial among 150 infertile women undergoing IUI, demonstrated significantly higher serum progesterone levels in patients treated with oral dydrogesterone compared to intra-vaginal MCP (52.6±29.9 versus28.9±15.9, p=0.001) [24]. A lower abortion rate was observed for the dydrogesterone group compared to the vaginal MCP group (9.1% versus 15.8%), however, this finding was not statistically significant (p=0.056) [24]. Overall satisfaction rate was significantly higher in dydrogesterone group compared to vaginal MCP (85.1%

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versus 60.8%, p<0.001) [24]. Similarly, an open-label prospective study among 78 women reported higher pregnancy rates in dydrogesterone group compared to oral micronized progesterone (30% versus 11%) which can be attributed to increased mid luteal progesterone level (30.7 ng/ml versus 20.6 ng/ml) that contributes in the sustenance of the pregnancy [25]. Furthermore, safety and tolerability of oral, intra-vaginal micronized progesterone, and oral dydrogesterone has been observed to be similar with limited serious adverse events or birth defects reported [25,26]. However, findings from a meta-analysis of five RCTs, reports multiple pregnancies in the intra-vaginal progesterone group (13 events of 951 cycles) as well as miscarriages (68 miscarriages of 951 cycles) compared to the no progesterone group (multiple pregnancy 12 events and miscarriages 52 of 951 cycles) [27].

Role of Progestogens in in-vitro fertilization cycles (IVF)

For luteal support in ART, exogenous progesterone is associated with a significantly higher pregnancy rate than placebo or no treatment. Findings from randomized comparative studies published in recent literature have also demonstrated similar clinical efficacy for both oral dydrogesterone and intra-vaginal MCP in IVF cycles indicating that these medications, when compared with each other, show no significant difference in successful clinical pregnancy rates [28-32] (Table 1). Currently available formulations of progesterone include oral, rectal, intra-vaginal, and intra-muscular.

Author	Study Design	Study Sample	Treatment Arms	Clinical Efficacy Outcomes	
				Intervention	Comparator
Dydrogesterone versus Micronized progesterone					
Chakravarty et al. 2005 [28]	Prospective randomized comparative study	430	Dydrogesterone versus vaginal micronized progesterone	Viable delivery: 24.1%	Viable delivery: 22.8%
				Miscarriage: 7.6%	Miscarriage: 8.3%
Saharkhiz et al. 2005 [29]	Randomized comparative study	210	Dydrogesterone versus vaginal micronized progesterone	Ongoing pregnancy rate:30.0%	Ongoing pregnancy rate:30.0%
				Implantation: 22.0%	Implantation: 24.0%
				Multiple pregnancy rate: 5.30%	Multiple pregnancy rate: 7.20%
				Miscarriage rate: 5.0%	Miscarriage rate: 3.0%
Tomic et al. 2015 [30]	Randomized control trial	853	Dydrogesterone versus vaginal micronized progesterone	Ongoing pregnancy rate: 30.3%	Ongoing pregnancy rate: 28.1%
Ganesh et al. 2011 [31]	Prospective randomized study	1,373	Dydrogesterone versus vaginal micronized progesterone (gel) versus vaginal micronized progesterone (capsule)	Pregnancy rate: 28.67%	Vaginal micronized progesterone (gel)
				Miscarriage rate: 11.57%	Pregnancy rate: 28.63%
					Miscarriage rate: 13.04%
					Vaginal micronized progesterone (capsule)
Salehpour et al. 2013 [64]	Prospective, single blinded, randomized clinical trial	80	Dydrogesterone versus vaginal micronized progesterone	Clinical pregnancy rate: 25%	Clinical pregnancy rate: 32.5%
				Miscarriage: 7.5%	Miscarriage: 7.7%

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Barbosa et al. 2015 [32]	Review & Meta-analysis	Ongoing pregnancy: N=3,134 women Clinical pregnancy: N=3,809 women	Dydrogesterone versus vaginal progesterone	No significant difference observed between oral dydrogesterone and vaginal progesterone Ongoing pregnancy: Risk ratio: 1.04, 95% CI 0.92-1.18, Clinical pregnancy: Risk ratio: 1.07, 95% CI 0.93-1.23 Miscarriage:	
Domitrz et al. 1999 [65]	Retrospective study	518	Dydrogesterone versus intramuscular progesterone	Similar pregnancy rate, implantation rate and spontaneous abortion rate observed in both the groups	
17-Hydroxyprogesterone caproate (17-OHPC)					
Abate et al. 1997 [50]	Randomized comparative study	80	17-OHPC versus intramuscular progesterone	17 OH-PC showed higher pregnancy rates as compared to natural progesterone.	
Costabile et al. 2001 [43]	Prospective randomized study	300	17-OHPC versus intramuscular progesterone	Clinical preganacy: 44.7% Ongoing pregnancy: 42% Miscarriage: 3.5%	Clinical preganacy: 43.3% Ongoing pregnancy: 40.1% Miscarriage: 4.4%
Moini et al. 2011 [51]	Prospective randomized study	103	17-OHPC versus intramuscular progesterone	Ongoing pregnancy: 24.5% Live birth rate: 24.5% Abortion rate: 7.1%	Ongoing pregnancy: 20%% Live birth rate: 18% Abortion rate: 35.5%
Abate et al. 1999 [50]	Randomized study	86	17-OHPC versus placebo	Pregnancy rate: 32.5%	Pregnancy rate: 18.3%
Abu-Musa et al. 200866	Randomized control study	125	17-OHPC versus control	Clinical pregnancy: 34.9%	Clinical pregnancy: 38.7%
Unifer et al. 2004 [52]	Prospective randomized study	320	17-OHPC versus vaginal progesterone	17 OH-PC is found to be more effective in IVF-embryo transfer cycles compared to vaginal progesterone.	
Satir F et al. 2013 [53]	Retrospective single centre study	927	17-OHPC versus intravaginal micronized progesterone	Clinical pregnancy rate: Odds ratio 1.66, 95%CI 1.07-2.60, p=0.03 On-going pregnancy rate: Odds ratio 1.43, 95%CI 0.89-2.30, p=0.14	

Table 1: Clinical efficacy of progestogens.

Several clinical trials have demonstrated that among the different routes of progesterone administration, the intra-vaginal route is considered to be more effective than the IM or oral route. In most ART centers worldwide the use of intra-vaginal Progestogen has become routine practice, however, several research papers also report that intra-vaginal route is not very well accepted due to side effects such as vaginal irritation and discharge [33].

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Route of Progestogen administration

Oral administration: Oral MCP was commonly used for luteal support in IVF cycles during the late 1980's however, the results observed with its use have been poor due to absence of secretory transformation of the endometrium in patients with premature ovarian failure who had been treated with oral MCP when compared with IM injections or intra-vaginal MCP [34]. This finding suggested that oral administration of MCP had possibly reduced the hormone's bioavailability. Additionally, a randomized prospective clinical trial among 43 women undergoing IVF who were treated with oral MCP and progesterone (IM) reported lower clinical pregnancy rates (45.8% versus 57.9%) and implantation rates (18.1% versus 40.9%) for the oral MCP group. Thereby indicating that oral MCP is less effective compared to progesterone (IM) [35].

To overcome this problem, dydrogesterone, a retro-progesterone, through its preferential affinity for progesterone receptor, has a better potential to generate endothelial nitric oxide syntheses (ENOS) and release nitric oxide, thereby enhancing endometrial vascularity similar to natural progesterone [36]. The chemical configuration of dydrogesterone makes it metabolically stable and orally effective, as compared to intra-vaginal micronized progesterone [37]. Moreover, mean serum progesterone levels have also been reported to be higher when patients are given oral dydrogesterone than with intra-vaginal progesterone [38]. This is supported by a phase II randomized controlled study involving 675 patients undergoing ART (divided into 3 groups) randomized between dydrogesterone 30mg/day and intra-vaginal MCP 600mg/day that reported significantly higher pregnancy rates with dydrogesterone than with intra-vaginal MCP in all the three groups. (39.1% versus 26.7%; $p<0.01$, 41.2% versus 35.6%; $p<0.01$ and 48.2% versus 33.9%; $p<0.001$) [39].

Similar results were obtained from a randomized comparative study among 430 women undergoing IVF/ICSI, that reported comparative pregnancy and miscarriage rates with oral dydrogesterone and intra-vaginal MCP (24.1% versus 22.8%; 7.6% versus 8.6%), respectively [37]. A recent meta analysis also reported no difference in ongoing pregnancies (RR 1.04, 95% CI 0.92 to 1.18, I(2) = 0%, 7 RCTs, 3,134 women), clinical pregnancies (RR 1.07, 95% CI 0.93 to 1.23, I(2) = 34%, 8 RCTs, 3,809 women), and miscarriages (RR 0.77, 95% CI 0.53 to 1.10, I(2) = 0%, 7 RCTs, 906 clinical pregnancies) between oral dydrogesterone and intra-vaginal progesterone [32]. Furthermore, findings from a prospective randomized study conducted among 1,373 Indian women undergoing IVF/ICSI indicated comparable pregnancy rates among oral dydrogesterone, intra-vaginal MCP gel and intra-vaginal MCP capsule (28.67%, 28.63%, and 22.65% respectively). Also, comparable miscarriage rates were observed among the three groups (11.57%, 13.04% and 18.26% respectively) [31]. These findings are further supported in two other randomized comparative studies that have reported similar pregnancy and miscarriage rates between women receiving oral dydrogesterone and intra-vaginal MCP [29,30]. Thus based on the findings of these studies it can be concluded that oral dydrogesterone as luteal support in IVF is equally effective as intra-vaginal MCP.

Intra-vaginal and Intramuscular administration: The relative effectiveness of intra-vaginal and IM routes of progesterone supplementation has been controversial. The intra-vaginal route of progesterone supplementation in IVF has gained wide application as a first choice of luteal support regimen, mainly due to its clinical effectiveness. Following intra-vaginal administration of progesterone, high uterine progesterone concentrations with low peripheral serum values are observed due to uterine first pass effect where liver metabolization is absent [40-42]. With IM progesterone; supplementation is given as an injection of natural progesterone in oil. However, this route is associated with a number of local side effects, including pain, inflammatory reactions, and abscesses at the site of injection, causing a lack of enthusiasm for this treatment modality [43]. In addition, many reports have been published in which patients receiving IM progesterone have developed acute eosinophilic pneumonia [44, 45]. These drug induced conditions show that the use of IM progesterone can be associated with morbidity in otherwise healthy women.

A clinical trial involving 250 women in a first IVF cycle, randomized to receive IM progesterone or intra-vaginal micronized progesterone observed higher pregnancy rates in the group treated with IM progesterone [46]. A second open label randomized trial involving 201 women yielded similar results with age adjusted odds ratio for clinical pregnancy, implantation, and live birth rates favoring the IM progesterone treatment arm as opposed to the intra-vaginal (gel) progesterone arm [47]. In contrast, an open-label trial with 1,184 women from 16 US centers between intra-vaginal and IM progesterone reported comparable clinical (35.1% versus 35.2%,

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respectively) and ongoing pregnancy rates (30.2% versus 33.6%, respectively) between the two treatment groups. Similarly, a retrospective cohort study among 544 women treated with intra-vaginal MCP and progesterone (IM) reported no significant differences in the rate of clinical pregnancies (49% versus 53%), on-going pregnancies (44% versus 47%), miscarriages (8% versus 10%) and implantations (30% versus 29%) [48]. Findings from a meta-analysis analyzing data from four studies published in 2010 comparing IM progesterone versus intra-vaginal progesterone in 1,222 women undergoing IVF cycles reported no difference in live-birth rate with an odds ratio of 0.85 (95% CI 0.66-1.10) On the basis of presented recent evidence, intra-vaginal administration of progesterone can be considered as a viable alternative to IM progesterone injections as luteal support [49].

Another progesterone, 17 alpha-hydroxyprogesterone caproate (17 OH-PC) administered intramuscularly for luteal phase support is commonly used and has shown better pregnancy rates as compared to IM progesterone [50]. This is supported by findings from two prospective randomized studies which reported higher pregnancy rates and lower abortion rates in 17 OH-PC groups compared to the IM progesterone group [43, 51]. In addition, when 17 OH-PC IM was compared to intra-vaginal progesterone it showed similar to slightly better efficacy at providing luteal support [52,53]. Overall, 17 OH-PC IM is better or equally effective in providing LPS as compared progesterone IM and intra-vaginal progesterone though findings were not statistically significant.

Rectal administration: Finally, there are a number of publications that have evaluated the rectal use of natural progesterone in women undergoing IVF [54,55]. Chakmakijan and Zachariah (1987) studied the bioavailability of micronized progesterone by measuring sequential serum progesterone concentrations after a single bolus of 50 – 200 mg given sublingually, orally (capsule and tablet), vaginally and rectally (suppositories) during the follicular phase of a group of normally menstruating women. When compared with other modes of administration, rectal application resulted in serum concentration during the first 8 h twice as high as other forms. However, to the best of our knowledge, there are no prospective randomized trials to compare the rectal administration of progesterone with other administration routes for IVF.

Overall safety profile of progestogens in IVF: Several studies have reported good patient compliance and fewer side effects with oral dydrogesterone, when compared to intra-vaginal micronized progesterone [28,31] (Table 2). Findings from a recent randomized control trial report significantly higher overall satisfaction and tolerability with oral dydrogesterone when compared with intra-vaginal progesterone gel [27]. Additionally, no birth defects have been observed with the use of dydrogesterone [56, 57]. Intra-vaginal progesterone gel has been reported to lead to vaginal bleeding, interference with coitus and local adverse effects such as vaginal irritation and discharge [28]. Oral micronized progesterone when compared with intra-vaginal progesterone leads to fatigue, dizziness, headaches, faintness and urinary frequency [58]. Furthermore, intramuscular progesterone includes several complications such as sterile abscesses, bleeding into the muscle and pain at injection site [59]. Therefore, oral dydrogesterone can be considered a safe and efficacious alternative to intra-vaginal and IM progesterone as luteal phase support in ART.

Author	Study Design	Study Sample	Treatment Arms	Safety Profile Outcomes
Chakravarty et al. 2005 [28]	Prospective randomized comparative study	430	Dydrogesterone vs. vaginal micronized progesterone	No vaginal irritation and discharge with dydrogesterone
Ganesh et al. 2011 [31]	Prospective randomized, single-blinded comparative study	1,373	Dydrogesterone vs vaginal micronized progesterone	Patient compliance, vaginal irritation and discharge can be avoided with dydrogesterone
Queisser-Luft, 2009 [57]	Retrospective observational study	28	Dydrogesterone alone	No congenital malformation associated with dydrogesterone observed
Balasch et al. 1982 [56]	Randomized comparative study	44	Dydrogesterone vs. vaginal progesterone	No congenital malformations noted

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Arafat et al. 1988 [67]	Unknown	8	Oral micronized progesterone alone	Sedative, hypnotic effect
Norman et al. 1991 [58]	Randomized trial	10	Oral micronized progesterone	Fatigue, dizziness, headaches, faintness and urinary frequency, mild side effect related to central nervous system
Tomic et al. 2014 [30]	Randomized control trial	853	Vaginal progesterone vs. dydrogesterone	Vaginal bleeding, interference with coitus, vaginal irritation and discharge
Ng et al. 2007 [68]	Randomized trial	132	Vaginal progesterone suppositories vs. vaginal progesterone tablet	Perineal irritation, yeast infection
Check et al. 2009 [59]	Review	-	Intramuscular progesterone in oil	Sterile abscesses, bleeding into the muscle and pain at injection site [58]

Table 2: Safety profile of progestogens.

Conclusion

Progesterone production from the corpus luteum is critical for natural reproduction. Luteal phase deficiency in natural cycles is a plausible cause of infertility and pregnancy loss, though there is no adequate diagnostic test to detect this. Progesterone supplementation is an important aspect of assisted reproductive technology treatment and has demonstrated clinical benefits in promoting fertility, preventing miscarriages and even preventing pre-term labor [58]. Available evidence from the literature suggests that the most common forms of progesterone supplementation are safe to be used in early pregnancy. The FDA conducted a thorough review of the relevant published studies, and they found that there is no increase in congenital anomalies including genital abnormalities in male or female infants resulting from maternal exposure to progesterone or 17 α-hydroxyprogesterone in early pregnancy [60]. Though there are several guidelines that recommend the use of progesterone as luteal phase support in ART, the route of administration that leads to optimal pregnancy outcomes remains a subject of ongoing debate. Progestogens have different pharmacokinetic and pharmacodynamic properties when used in different routes of administration. Although intramuscular progesterone in oil generates high serum levels of progesterone, intra-vaginal administration results in very high local progesterone concentration in endometrial tissue [40-42]. While different researchers have made conclusions about the superiority of intramuscular or intra-vaginal progesterone, a recent Cochrane systematic review of clinical trials concluded that with IVF cycles, similar pregnancy rates were observed with intramuscular or intra-vaginal routes of progesterone administration [49]. The similar efficacy of intra-vaginal and IM progesterone, combined with patient preference and lower side effect profile of intra-vaginal progesterone supplementation over IM in IVF cycles, explains the increasing popularity of intra-vaginal supplementation [61].

Oral progesterone as luteal support is also gaining popularity in ART, due to its ease of administration, good pharmacokinetic /bioavailability profile, comparable pregnancy rates, fewer local side effects, and better patient convenience compared with intra-vaginal micronized progesterone. These findings have been supported in recent meta-analysis and randomized controlled studies [32,37,39]. In addition, dydrogesterone is the only drug that has been approved for use in several indications that include but are not limited to threatened miscarriage, recurrent miscarriage, infertility due to luteal deficiency, etc [62,63]

In conclusion, based on review of the current literature, intra-vaginal progesterone and oral dydrogesterone have shown to be clinically effective and safe as luteal supplementation in IVF cycles. However, much of the current scientific evidence is based on reviews and meta-analyses of observational studies and on few RCTs, therefore future investigations with longer follow-ups and larger sample sizes comparing different routes of administration, dosages, and timing of administration are warranted.

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Intra-uterine insemination

- *Dydrogesterone (oral) shows greater (85%) satisfaction level compared to intra-vaginal MCP (61%) [24].*
- *Dydrogesterone (oral) exhibits a higher pregnancy rate compared to oral MCP (30% versus 11%) [25].*

In vitro fertilization

- *Oral MCP is not as effective as intra-vaginal or IM progesterone as luteal support in IVF cycles [34, 35].*
- *Oral dydrogesterone showed similar pregnancy and miscarriage rates when compared to intra-vaginal MCP as luteal support in IVF cycles [28-32, 37].*
- *Intra-vaginal progesterone can be considered a viable alternative to IM progesterone injections for luteal support [47-49].*
- *No serious adverse events or congenital abnormalities were observed in new born of mothers who received progesterone in clinical studies [70].*

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